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Graphical Abstract

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Iodine-promoted Direct Thiolation(Selenylation) of Imidazole with Disulfides(Diselenide): A Convenient and Metal-Free Protocol for Synthesis of 2-Arylthio(seleno)imidazole

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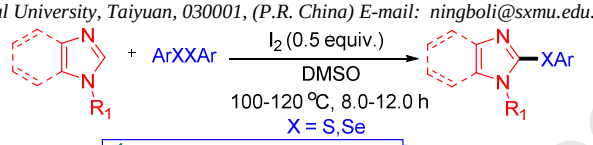

- Metal-free reaction
- Good to excellent yields
- Wild functional group tolerance

31 examples, yield up to 99%

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Iodine-promoted direct thiolation (selenylation) of imidazole with disulfides (diselenide): a convenient and metal-free protocol for the synthesis of 2-arylthio(seleno)imidazole

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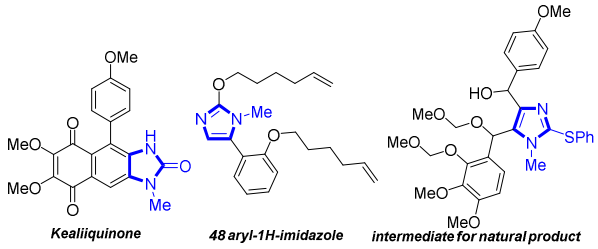
ABSTRACT

A convenient and metal-free protocol for the synthesis of 2-arylthio(seleno)imidazoles from imidazoles and disulfides (diselenides) was developed through the direct thiolation (selenylation) of imidazoles promoted by 0.5 equiv. of iodine. This process is scalable and tolerates a wide spectrum of disulfides (diselenides) to deliver products in high yields. Compared with previous methods, this protocol has the advantages of a simple operation, wide functional group tolerance and good yields, providing an efficient route to 2-arylthio(seleno)imidazoles, which are key structural scaffolds of many natural products.

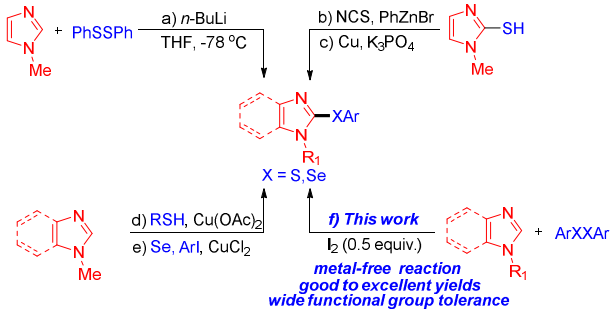
1. Introduction

Imidazole derivatives are common structural motifs in many natural products and drugs,[1-3] such as kealiiquinone,[4] naamidine A[5] and clathridine A,[6] which show anti-cancer activity. Some intermediate for natural product[7] can be synthesized by imidazole derivatives. In addition, 48 aryl-1*H*-imidazole compounds displayed similar *in vitro* growth inhibition in cancer cells, and were found to be cytostatic in melanoma cell line (Scheme 1).[8] The aforesaid compounds and other medicines possessing therapeutic potential can be synthesized from imidazoles, especially 2-arylthio(seleno)-1*H*-imidazole and its derivatives.[9,10]



Scheme 1. Bioactive molecules with the imidazole motif.

Because of the important application of 2-arylthio(seleno)-1*H*-imidazole derivatives in the synthesis of many natural products and medicinal agents,[11] efforts are devoted toward their generation.[12] Various methods for the synthesis of 2-arylthio(seleno)-1*H*-imidazole derivatives have been reported.[13] However, some of these methods must be performed under harsh conditions owing to the use of organometallic reagents such as *n*-BuLi and C_6H_5ZnBr, which are highly sensitive to water (Scheme 2a and 2b).[14,15] In addition, the toxic and odorous thiols or mercaptan (as starting reagents) must be used in other methods (Scheme 2b-2d).[16] Recently, Wu *et al.* reported an effective method for the synthesis of 2-arylseleno-1*H*-imidazole by the three-component coupling reaction of electron-deficient heterocycles, Se powder and aryl iodides catalyzed by copper chloride (Scheme 2e).[13a] Nevertheless, this process requires a high temperature and nitrogen protection. Furthermore, all of the abovementioned catalytic systems must use metal catalysts.



Scheme 2. General methods for the synthesis of 2-arylthio(seleno)imidazoles.

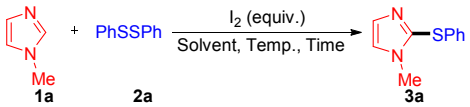
Up to now, a metal-free catalysis for the synthesis of 2-arylthio(seleno)-1*H*-imidazole has not been reported. Therefore,

as an environment-friendly and less expensive methodology, the development of transition-metal-free systems for the synthesis of 2-arylthio(seleno)-1*H*-imidazole derivatives, which are ubiquitous scaffolds,[17] is highly desired. Diaryl disulfides(diselenides), which are known to be air-stable, free of smell, and good electrophilic reagents with low toxicity, have been used often in the arylthiolation and arylselenylation.[18] Iodine reagents have also been used in C-S bond formation.[19,20] As a part of our research program in the synthesis of sulfur-containing compounds,[21,22] we report an iodine-mediated direct thiolation(selenylation) of imidazole with diaryl disulfides (diselenides) for synthesis of 2-arylthio(seleno)-1*H*-imidazole, which is in sharp contrast to the transition-metal-catalyzed reactions (Scheme 2f).

2. Results and discussion

We used the thiolation of 1-methylimidazole (**1a**) with diphenyl disulfide (**2a**) as a model reaction to optimize the reaction parameters, and the results are summarized in Table 1.

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3a**

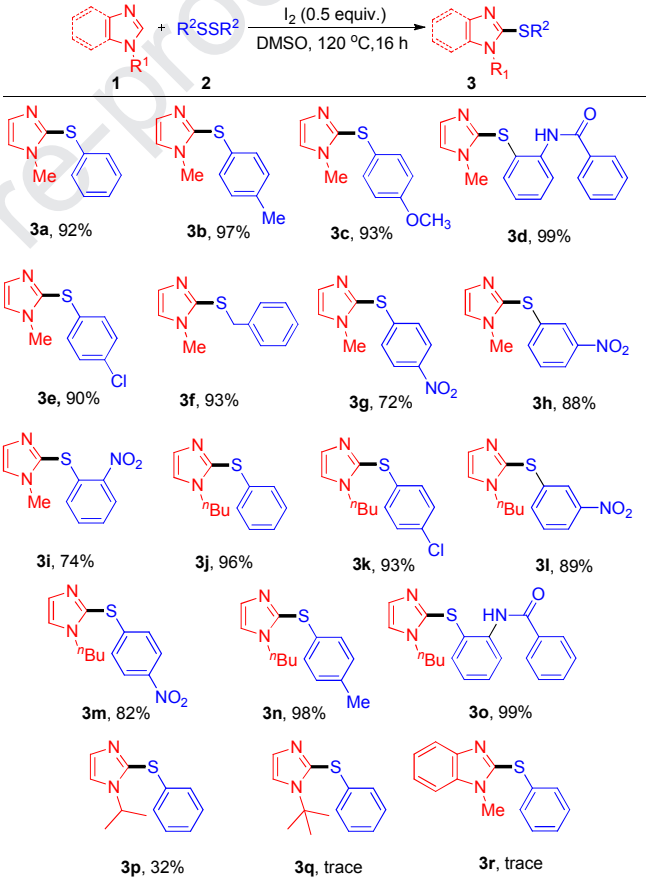
Entry	Additive (equiv.)	Temp. (°C)	Solvent	Time (h)	Yield (%)[b]
1	I_2 (1.0)	60	DMSO	12	32
2	I_2 (1.0)	80	DMSO	12	53
3	I_2 (1.0)	100	DMSO	12	77
4	I_2 (1.0)	120	DMSO	12	88
5	I_2 (1.0)	130	DMSO	12	83
6	I_2 (1.0)	150	DMSO	12	37
7	I_2 (1.0)	120	Toluene	12	24
8	I_2 (1.0)	120	THF	12	35
9	I_2 (1.0)	120	MeCN	12	47
10	I_2 (1.0)	120	DMF	12	69
11	I_2 (1.0)	120	1,4-dioxane	12	52
12	TBHP (2.0)	120	DMSO	12	21
13	DTBP (2.0)	120	DMSO	12	19
14	BPO (2.0)	120	DMSO	12	28
15	CuBr (2.0)	120	DMSO	12	11
16	CuI (2.0)	120	DMSO	12	24
17	NH_4I (2.0)	120	DMSO	12	*N. D.*[c]
18	none	120	DMSO	12	*N. D.*[c]
19	I_2 (0.5)	120	DMSO	12	84
20	I_2 (0.3)	120	DMSO	12	76
21	**I_2 (0.5)**	**120**	**DMSO**	**16**	**92 (90)[d]**
22	I_2 (0.3)	120	DMSO	20	82

[a] Reaction conditions: 1-methyl-1*H*-imidazole (**1a**) (0.5 mmol), diphenyl disulfide (**2a**) (0.25 mmol), iodine, solvent (2.0 mL), in air; [b] GC yields; [c] N.D. for not detected; [d] Isolated yields.

Analyzing Table 1, we can see that the desired product 1-methyl-2-(phenylthio)-1*H*-imidazole (**3a**) was obtained with a yield of 32% via the thiolation of 1-methylimidazole (**1a**) and diphenyl disulfide (**2a**) in the presence of 1.0 equiv. of iodine (I_2) at 60 °C (Table 1, entry 1). We then explored the influence of temperature on the reaction by varying the temperature from 60 to 150 °C (Table 1, entries 1-6), and the results showed that 120 °C was the best temperature for giving the desired product with a yield of 88% (Table 1, entry 4). The screening of solvents (Table 1, entries 4 and 7-11) revealed that DMSO was the best solvent (Table 1, entry 4, 88%), mainly because of its excellent solubility to reactants and oxidability to the sulfenylation. Other oxidants such as TBHP, DTBP, BPO, CuBr, CuI and NH_4I were also investigated, and low or poor yields were obtained (Table 1, entries 4, 12-17). No desired product was observed without additives (Table 1, entry 18). Lastly, we explored the influence of the additive amount for sulfenylation. We found that 0.5 equiv. of iodine was enough to promote the sulfenylation effectively by extending the reaction time to 16 hours (Table 1, entry 21). A lower yield of 82% was obtained when the oxidant amount was decreased to 0.3 equiv. despite extending the reaction time to 20 hours (Table 1, entry 22). After extensive screening, we found that the sulfenylation of 1-methylimidazole (**1a**) and diphenyl disulfide (**2a**) in DMSO promoted by 0.5 equiv. of iodine in air provided the desired product with an excellent yield of 92% within 16 hours.

To demonstrate the efficiency of the sulfenylation, we explored the generality of our method by extending the optimal conditions to various substituted imidazoles and diaryl disulfides, and the results are summarized in Table 2.

Table 2. The sulfenylation of 1-alkyl-1*H*-imidazoles with diaryl disulfides.[a, b]



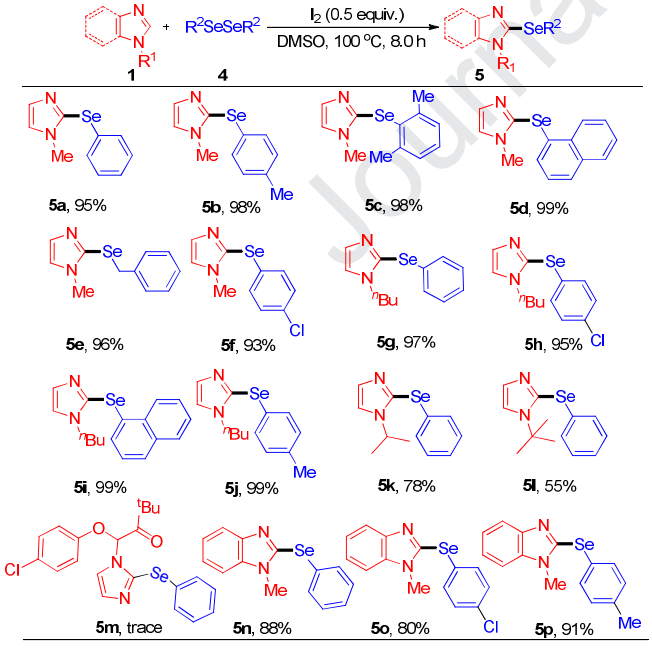
[a] Reaction conditions: 1-alkane-1*H*-imidazoles (**1**) (0.55 mmol), diaryl disulfides (**2**) (0.25 mmol), iodine (0.125 mmol), DMSO (2.0 mL), 120 °C, 16 h, in air. [b] Isolated yields.

A variety of diaryl disulfides could efficiently undergo sulfenylation to afford the corresponding products with good to excellent yields (**3a**-**3i**, 72-99%). Electron-donating groups (*e.g.*, Me and OCH_3) or electron-withdrawing groups (*e.g.*, Cl and NO_2) on the benzene ring of the diaryl disulfides slightly affected the sulfenylation, and provided the corresponding products in good to excellent yields. Notably, this protocol is also applicable to the diphenyl disulfide-containing amide group, which gave the desired product **3d** with a 99% yield. When *N*-butyl-1*H*-imidazole reacted with diaryl disulfides, all

corresponding products were obtained in excellent yields (**3j**-**3o**, 82-99%). The steric effect of *N*-^{i}Pr and *N*-^{t}Bu at the 1-position of 1-alkane-1H-imidazole was significant (**3p** and **3q**, 32% and trace amount). The yield of desired product **3r** was obtained in trace amounts when 1-methylbenzimidazole was treated with diphenyl disulfide under standard conditions. However, alkyl disulfides (such as dipropyl disulfide and diisobutyl disulfide) plausibly failed to yield desirable products because they easily formed ionic liquids.

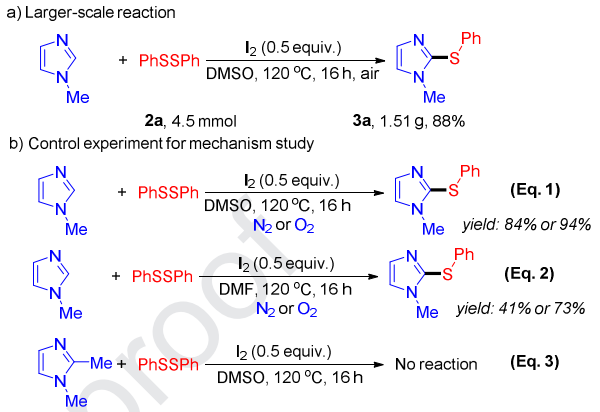
Encouraged by the successful synthesis of 2-arylthioimidazole, we decided to expend this strategy to the selenation of imidazoles under milder reaction conditions (100 ^{o}C, 8.0 h), and the results are summarized in Table 3. Analyzing Table 3, we can see that electron-donating and electron-withdrawing functional groups at the *o*- and *p*-positions of the diaryl selenides slightly affected the selenation, affording the corresponding products with excellent yields (Table 3, **5a**-**5f**, 93%-99%). When *N*-butyl-1*H*-imidazole reacted with diaryl diselenides, all corresponding products were obtained in excellent yields (**5g**-**5j**, 95-99%). The steric effect of *N*-^{i}Pr and *N*-^{t}Bu at the 1-position of 1-alkane-1H-imidazole was slightly less than that of the reaction with diphenyl disulfide (**5k** and **5l**, 78% and 55%).However, only a trace yield was observed when an imidazole with a bulky substituent at N-atom position was used as the substrate (**5m**). In addition, the reaction can also be applied to 1-methylbenzimidazole, which reacted with diaryldiselenides to afford the corresponding products in the yields of 80-91% (**5n**-**5p**).

Table 3. The selenation of 1-alkane-1*H*-imidazoles with diaryl diselenides.[a,b]



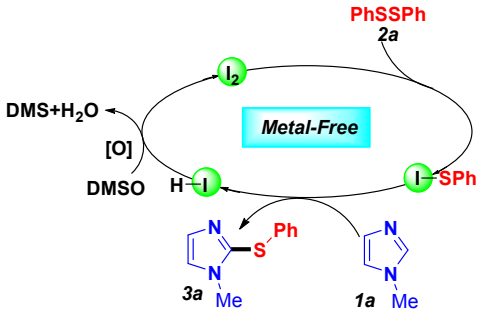
[a] Reaction conditions: 1-alkane-1*H*-imidazoles (**1**) (0.55 mmol), diaryl diselenides (**2**) (0.25 mmol), iodine (0.125 mmol), DMSO (2.0 mL), 100 ^{o}C, 8.0 h, in air. [b] Isolated yields.

The sulfenylation can also be carried out on a larger scale reaction. The desired product (**3a**) was obtained with a yield of 88% when 10 mmol of 1-methylimidazole (**1a**) was treated with 4.5 mmol of diphenyl disulfide (**2a**) under the standard conditions (Scheme 3a). To shed light on the mechanism of the sulfenylation, 1-methylimidazole (**1a**) was treated with diphenyl disulfide (**2a**) with DMSO (Scheme 3b, Eq. 1) and DMF (Scheme 3b, Eq. 2) under a nitrogen and oxygen atmosphere. The yield of the desired product (**3a**) indicates that O_2 may be involved in the oxidation process during the whole sulfenylation. No reaction was observed when 1-methylimidazole was replaced by 1,2-dimethylimidazole, indicating the regioselectivity of this method (Scheme 3b, Eq. 3).



Scheme 3. (a) Larger-scale synthesis of **3a**; (b) Control experiments for mechanism study.

On the basis of the above experimental results and previous work,[21] a possible mechanism is depicted in Scheme 4. The first step is the generation of PhSI via the reaction of iodine with diphenyldisulfide at high temperature, which was detected by GC-MS. Meanwhile, the blank reaction was performed to verify the generation of PhSI (listed in SI). Then, the replacement reaction of the intermediate PhSI with 1-methylimidazole (**1a**) yielded the desired product (**3a**) and HI, which was then converted to I_2 via the oxidation of DMSO and oxygen from air.



Scheme 4. Proposed mechanism for sulfenylation.

3. Conclusion

In summary, we have developed a metal-free and convenient protocol for the synthesis of 2-arylthio(seleno)imidazoles *via* the sulfenylation(selenylation) of imidazoles with disulfides(diselenides) promoted by 0.5 equiv. of iodine. A broad range of diaryldisulfides or diaryldiselenides were tolerated, and all desired products could be obtained in good to excellent yields, providing a convenient and general way to synthesize 2-arylthio(seleno)imidazoles.

4. Experimental Section

Unless noted, all reactions were conducted in Schlenk tubes under an atmosphere of air using commercial solvents. Iodine,

1-methylimidazole, 1-butylimidazole, 1-methylbenzimidazole, diphenyl disulfide, 4,4'-dichlorodiphenyl disulfide, 4-methylphenyl disulfide, bis(2-benzamidophenyl) disulfide, dibenzyl disulfide, 4,4'-dinitrodiphenyl disulfide, 3,3-dinitrodiphenyl disulfide, 2,2'-dinitrodiphenyl disulfide were purchased from Energy company and used as received. Diphenyl diselenide, di(4-methylphenyl) diselenide, di(4-chlorophenyl) diselenide, dinaphthyl diselenide, dibenzyl diselendide and di(2,6-dimethylphenyl) diselenide were synthesized according to the previous work.[23]

4.1 Analytical methods

Thin-layer chromatography (TLC) analysis was carried out using gel 60 F_{254} pre-coated plates. Visualization was accomplished with UV lamp or I_2 stain. Silica gel 300-400 mesh size was used for column chromatography using the combination of ethyl acetate and hexane as an eluent. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz. Chemical shift were recorded in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ^{1} HNMR splitting patterns are designated as singlet (s), doublet (d), double doublet (dd), triplet (t) or multiplet (m). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 MHz. ^{1}H NMR and ^{13}C NMR spectra were recorded using residue solvent peaks as internal standards ($CHCl_3$, δ = 7.26 ppm for ^{1}H, δ = 77.0 ppm for ^{13}C; DMSO, δ = 2.5 ppm for ^{1}H, δ = 39.5 ppm for ^{13}C). Coupling constants are given in hertz. Mass spectra (MS) were obtained using EI mass spectrometer.

4.2 Experimental Procedure for 3a and characterization data of 3a-3p

Typical procedure for the synthesis of 1-Methyl-2-(phenylthio)-1H-imidazole **3a**: 1-methyl-1H-imidazole **1a** (45.2 mg, 0.55 mmol) was added drowpwise to a solution of diphenyldisulfane **2a** (54.6 mg, 0.25 mmol) and I_2 (31.7 mg, 0.125 mmol) in 2.0 mL of DMSO. Then the mixture was stirred at 120 ^{o}C for 16 hours. Then the reaction mixture was evaporated in vacuum, and the desired product **3a** was obtained by silica gel column chromatography using ethyl acetate/hexane as an eluent in the yield of 92% (87.4 mg).

1-methyl-2-(phenylthio)-1H-imidazole (3a)[16]: Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.4). The title compound was obtained as a colorless liquid (92%, 87.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.21 (m, 2H), 7.16-7.11 (m, 4H), 7.06 (s, 1H), 3.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.95, 134.92, 130.14, 129.26, 127.92, 126.56, 123.92, 33.87; MS (m/z): 191.0 (M^+).

1-methyl-2-(p-tolylthio)-1H-imidazole (3b)[1c]: Isolated by flash column chromatography (petroleum ether/ethyl acetate = 3/1, R_f = 0.3). The title compound was obtained as a colorless liquid (97%, 99.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.39 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 3.53 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.79, 137.89, 136.15, 132.65, 129.98, 126.89, 31.56, 20.91; MS (m/z): 205.1 (M^+).

2-((4-methoxyphenyl)thio)-1-methyl-1H-imidazole (3c):[17c] Isolated by flash column chromatography (petroleum ether/ethyl acetate = 1/1, R_f = 0.4). The title compound was obtained as a yellow oil (93%, 102.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H), 7.15 (s, 1H), 7.03 (s, 1H), 6.86-6.84 (m, 2H), 3.80 (s, 3H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.17, 139.75, 131.65, 129.79, 124.36, 123.36, 114.93, 55.35, 33.82; MS (m/z): 221.0 (M^+).

N-(2-((1-methyl-1H-imidazol-2-yl)thio)phenyl)benzamide (3d): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 3/1, R_f = 0.4). The title compound was obtained as a yellow solid (99%, 152.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.30 (d, *J* = 4.0 Hz, 3H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.54-7.51 (m, 3H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.10-7.05 (m, 2H), 6.95 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.07, 141.28, 139.57, 135.05, 134.67, 131.77, 130.70, 129.21, 128.50, 128.16, 124.67, 124.58, 123.34, 122.09, 33.95; HRMS (ESI): [M + H]$^+$ calcd for [$C_{17}H_{15}N_3OS$]: 309.0942, found: 309.0937.

2-((4-chlorophenyl)thio)-1-methyl-1H-imidazole (3e): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.4). The title compound was obtained as a colorless liquid (90%, 100.8 mg); ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.24-7.20 (m, 3H), 7.12-7.08 (m, 3H),3.65 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 137.64, 133.14, 132.85, 130.15, 129.55, 129.44, 123.97, 33.92; HRMS (ESI): [M + H]$^+$ calcd for [$C_{10}H_9ClN_2S$]: 224.0181, found: 224.0172.

2-(benzylthio)-1-methyl-1H-imidazole (3f)[13c]: Isolated by flash column chromatography (petroleum ether/ethyl acetate = 1/1, R_f = 0.6). The title compound was obtained as a yellow solid (93%, 95.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 5H),6.67 (s, 1H), 6.57 (s, 1H), 5.25 (s, 2H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.87, 135.86, 128.87, 128.30, 128.15, 118.03, 116.36, 51.35, 35.27; MS (m/z): 205.1 (M^+).

1-methyl-2-((4-nitrophenyl)thio)-1H-imidazole (3g): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.5). The title compound was obtained as a yellow solid (72%, 84.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.0 Hz, 2H), 7.21 (s, 1H), 7.12 (s, 1H), 7.01 (d, *J* = 7.6Hz, 2H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.00, 145.25, 135.11, 131.07, 126.51, 124.73, 124.32, 33.96; HRMS (ESI): [M + H]$^+$ calcd for [$C_{10}H_9N_3O_2S$]: 235.0421, found: 235.0415.

1-methyl-2-((3-nitrophenyl)thio)-1H-imidazole (3h)[13c]: Isolated by flash column chromatography (petroleum ether/ethyl acetate = 3/1, R_f = 0.3). The title compound was obtained as a yellow solid (88%, 103.9 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.8 Hz, 2H), 7.28 (s, 1H), 7.20 (s, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.95, 145.37, 135.06, 131.14, 126.43, 124.75, 124.31, 33.95; MS (m/z): 236.1 (M^+).

1-methyl-2-((2-nitrophenyl)thio)-1H-imidazole (3i): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 3/1, R_f = 0.4). The title compound was obtained as a yellow solid (74%, 87.0 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.32-7.27 (m, 2H), 7.21 (s, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.04, 136.82, 136.38, 134.15, 131.26, 127.73, 126.09, 126.00, 124.73, 33.93; HRMS (ESI): [M + H]$^+$ calcd for [$C_{10}H_9N_3O_2S$]: 235.0421, found: 235.0415.

1-butyl-2-(phenylthio)-1H-imidazole (3j): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.5). The title compound was obtained as a colorless liquid (96%, 111.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.19 (m, 6H), 7.09 (s, 1H), 4.00 (t, *J* = 7.2 Hz, 2H), 1.65-1.58 (m, 2H), 1.30-1.21 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 129.77, 129.26, 128.47, 126.83, 122.34, 99.99, 46.99, 32.81, 19.66, 13.50; HRMS (ESI): $[M + H]^+$ calcd for $[C_{13}H_{16}N_2S]$: 232.1040, found: 232.1032.

1-butyl-2-((4-chlorophenyl)thio)-1H-imidazole (3k)[24]: Isolated by flash column chromatography (petroleum ether/ethyl acetate = 3/1, R_f = 0.3). The title compound was obtained as a colorless liquid (93%, 123.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.41 (s, 1H), 7.21-7.13 (m, 4H), 3.95-3.93 (m, 2H), 1.61-1.58 (m, 2H), 1.27-1.24 (m, 2H), 0.87-0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.40, 139.38, 132.89, 130.41, 130.11, 129.47, 113.94, 45.94, 32.99, 19.66, 13.46; HRMS (ESI): $[M + H]^+$ calcd for $[C_{13}H_{15}ClN_2S]$: 266.0650, found: 266.0643.

1-butyl-2-((3-nitrophenyl)thio)-1H-imidazole (3l): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.4). The title compound was obtained as a yellow solid (89%, 123.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-8.00 (m, 1H), 7.97 (s, 1H), 7.44-7.43 (m, 2H), 7.27 (s, 1H), 7.18 (s, 1H), 4.04 (t, *J* = 7.2Hz, 2H), 1.70-1.63 (m, 2H), 1.31-1.22 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.62, 138.55, 135.26, 133.00, 131.10, 129.93, 123.12, 121.92, 121.26, 47.03, 33.00, 19.63, 13.49; HRMS (ESI): $[M + H]^+$ calcd for $[C_{13}H_{15}N_3O_2S]$: 277.0891, found: 277.0886.

1-butyl-2-((4-nitrophenyl)thio)-1H-imidazole (3m): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 3/1, R_f = 0.3). The title compound was obtained as a yellow solid (82%, 113.5 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0 Hz, 2H), 7.30 (s, 1H), 7.20-7.15 (m, 3H), 4.01 (t, *J* = 7.2 Hz, 2H), 1.71-1.63 (m, 2H), 1.31-1.22 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.96, 145.69, 134.46, 131.28, 126.47, 124.23, 123.31, 47.07, 33.01, 19.62, 13.48; HRMS (ESI): $[M + H]^+$ calcd for $[C_{13}H_{15}N_3O_2S]$: 277.0891, found: 277.0886.

1-butyl-2-(p-tolylthio)-1H-imidazole (3n): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.5). The title compound was obtained as a colorless liquid (98%, 120.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.15-7.13 (m, 2H), 7.10-7.06 (m, 3H), 3.99 (t, *J* = 7.6 Hz, 2H), 2.29 (s, 3H), 1.65-1.58 (m, 2H), 1.30-1.21 (m, 2H), 0.87 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.37, 137.01, 130.78, 130.00, 129.68, 129.12, 122.11, 46.90, 32.82, 20.99, 19.68, 13.52; HRMS (ESI): $[M + H]^+$ calcd for $[C_{14}H_{18}N_2S]$: 246.1197, found: 246.1194.

N-(2-((1-butyl-1H-imidazol-2-yl)thio)phenyl)benzamide (3o): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 1/1, R_f = 0.6). The title compound was obtained as a colorless liquid (99%, 173.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.19 (s, 1H), 8.31-8.26 (m, 3H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.56-7.50 (m, 3H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.11-7.08 (m, 2H), 6.97 (s, 1H), 4.12 (t, *J* = 7.6 Hz, 2H), 1.74-1.67 (m, 2H), 1.37-1.31 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.16, 141.39, 139.37, 134.96, 134.68, 131.72, 130.73, 128.90, 128.46, 128.19, 125.13, 124.73, 122.68, 121.79, 46.99, 33.12, 19.77, 13.60; HRMS (ESI): $[M + H]^+$ calcd for $[C_{20}H_{21}N_3OS]$: 351.1411, found: 351.1405.

1-isopropyl-2-(phenylthio)-1H-imidazole (3p): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 1/1, R_f = 0.4). The title compound was obtained as a yellow oil (32%, 34.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.41 (s, 1H), 7.24-7.21 (m, 2H), 7.16-7.12 (m, 1H), 7.05-7.03 (m, 2H), 4.57-4.50 (m, 1H), 1.36 (d, *J* = 6.8Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.34, 137.39, 137.01, 129.11, 126.21, 125.97, 47.10, 23.75; HRMS (ESI): $[M + H]^+$ calcd for $[C_{12}H_{14}N_2S]$: 218.0884, found: 218.0881.

4.3 Experimental Procedure for 5a and characterization data of 5a-5p

Typical procedure for the synthesis of 1-Methyl-2-(phenylseleno)-1H-imidazole **3a**: 1-methyl-1H-imidazole **1a** (45.2 mg, 0.55 mmol) was added drowpwise to a solution of diphenyl diselenide **4a** (78.1 mg, 0.25 mmol) and I_2 (31.7 mg, 0.125 mmol) in 2.0 mL of DMSO. Then the mixture was stirred at 100 ^{o}C for 8 hours. Then the reaction mixture was evaporated in vacuum, and the desired product **5a** was obtained by silica gel column chromatography using ethyl acetate/hexane as an eluent in the yield of 95% (113.1 mg).

1-methyl-2-(phenylselanyl)-1H-imidazole (5a): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.5). The title compound was obtained as a white solid (95%, 113.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.40 (s, 1H), 7.23-7.13 (m, 5H), 3.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.92, 139.00, 131.52, 129.47, 129.23, 126.76, 32.75; HRMS (ESI): $[M + H]^+$ calcd for $[C_{10}H_{10}N_2Se]$: 238.0015, found: 238.0007.

1-methyl-2-(p-tolylselanyl)-1H-imidazole (5b): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 3/1, R_f = 0.4). The title compound was obtained as a white solid (98%, 123.6 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.37 (s, 1H), 7.12 (d, *J* = 7.2 Hz, 2H), 7.03 (d, *J* = 7.2 Hz, 2H), 3.57 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.75, 138.73, 136.83, 130.24, 129.71, 127.54, 115.39, 32.72, 20.97; HRMS (ESI): $[M + H]^+$ calcd for $[C_{11}H_{12}N_2Se]$: 252.0172, found: 252.0166.

2-((2,6-dimethylphenyl)selanyl)-1-methyl-1H-imidazole (5c): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.5). The title compound was obtained as a white solid (98%, 129.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.16-7.05 (m, 4H), 3.46 (s, 3H), 2.52 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.32, 139.82, 136.63, 130.28, 128.77, 128.32, 32.76, 24.07; MS (m/z): HRMS (ESI): $[M + H]^+$ calcd for $[C_{12}H_{14}N_2Se]$: 266.0328, found: 266.0321.

1-methyl-2-(naphthalen-1-ylselanyl)-1H-imidazole (5d): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.4). The title compound was obtained as a colorless liquid (99%, 142.1 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.76-7.72 (m, 2H), 7.61-7.49 (m, 3H), 7.30-7.26 (m, 1H), 7.14-7.13 (m, 1H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.06, 139.18, 134.05, 132.34, 130.34, 128.74, 127.87, 127.60, 126.75, 126.47, 126.13, 125.49, 32.82; HRMS (ESI): $[M + H]^+$ calcd for $[C_{14}H_{12}N_2Se]$: 288.0172, found: 288.0167.

2-(benzylselanyl)-1-methyl-1H-imidazole (5e)[13c]: Isolated by flash column chromatography (petroleum ether/ethyl acetate = 3/1, R_f = 0.4). The title compound was obtained as a yellow solid (96%, 121.4 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 5H), 6.85 (s, 1H), 6.73 (s, 1H), 5.35 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.44, 128.95, 128.47, 128.36, 120.11, 118.50, 53.38, 37.31; MS (m/z): 253.0 (M^+).

2-((4-chlorophenyl)selanyl)-1-methyl-1H-imidazole (5f): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.5). The title compound was obtained as a brown solid (93%, 126.1 mg); ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.33 (s, 1H), 7.13-7.04 (m, 3H), 3.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.11, 139.20, 132.97, 131.75, 130.56, 129.70, 129.59, 129.11, 32.75; HRMS (ESI): $[M + H]^+$ calcd for $[C_{10}H_9ClN_2Se]$: 271.9625, found: 271.9617.

1-butyl-2-(phenylselanyl)-1H-imidazole (5g): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 1/1, R_f = 0.6). The title compound was obtained as a colorless liquid (97%, 135.7 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.40 (s, 1H), 7.20-7.14 (m, 5H), 3.93 (t, *J* = 7.2 Hz, 2H), 1.61-1.54 (m, 2H), 1.27-1.18 (m, 2H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.16, 139.06, 131.85, 129.38, 129.21, 126.75, 45.97, 32.97, 19.66, 13.46; HRMS (ESI): $[M + H]^+$ calcd for $[C_{13}H_{16}N_2Se]$: 280.0485, found: 280.0479.

1-butyl-2-((4-chlorophenyl)selanyl)-1H-imidazole (5h): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.4). The title compound was obtained as a colorless liquid (95%, 148.7 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.41 (s, 1H), 7.21-7.13 (m, 4H), 3.95-3.93 (m, 2H), 1.62-1.58 (m, 2H), 1.27-1.24 (m, 2H), 0.87-0.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.40, 139.38, 132.89, 130.41, 130.11, 129.47, 113.94, 45.94, 32.99, 19.66, 13.46; HRMS (ESI): $[M + H]^+$ calcd for $[C_{13}H_{15}ClN_2Se]$: 314.0095, found: 314.0087.

1-butyl-2-(naphthalen-1-ylselanyl)-1H-imidazole (5i): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.5). The title compound was obtained as a white solid (99%, 162.6 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.73-7.70 (m, 2H), 7.60-7.51 (m, 2H), 7.47 (s, 1H), 7.28-7.24 (m, 1H), 7.15-7.13 (m, 1H), 3.90 (t, *J* = 7.2 Hz, 2H), 1.57-1.48 (m, 2H), 1.21-1.11 (m, 2H), 0.75 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.44, 139.53, 134.00, 132.32, 130.82, 128.71, 127.85, 127.47, 126.67, 126.39, 126.07, 125.45, 45.99, 32.98, 19.65, 13.42; HRMS (ESI): $[M + H]^+$ calcd for $[C_{17}H_{18}N_2Se]$: 330.0641, found: 330.0635.

1-butyl-2-(p-tolylselanyl)-1H-imidazole (5j): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 3/1, R_f = 0.4). The title compound was obtained as a yellow liquid (99%, 150.0 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.39 (s, 1H), 7.13-7.06 (m, 4H), 3.95 (m, 2H), 2.30 (s, 3H), 1.60 (m, 2H), 1.25-1.24 (m, 2H), 0.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.03, 138.85, 136.77, 130.13, 129.61, 127.90, 114.80, 45.91, 32.98, 20.96, 19.68, 13.47; HRMS (ESI): $[M + H]^+$ calcd for $[C_{14}H_{18}N_2Se]$: 294.0641, found: 294.0634.

1-isopropyl-2-(phenylselanyl)-1H-imidazole (5k): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.4). The title compound was obtained as a yellow liquid (78%, 103.3 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.39 (s, 1H), 7.23-7.16 (m, 5H), 4.64-4.53 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.90, 137.24, 132.07, 130.27, 129.34, 129.03, 126.65, 48.21, 23.82; HRMS (ESI): $[M + H]^+$ calcd for $[C_{14}H_{18}N_2Se]$: 266.0328, found: 266.0322.

1-(tert-butyl)-2-(phenylselanyl)-1H-imidazole (5l): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 1/1, R_f = 0.5). The title compound was obtained as a yellow liquid (55%, 76.5 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 1.2 Hz, 1H), 7.44-7.42 (m, 2H), 7.32-7.31 (m, 1H), 7.26-7.17 (m, 3H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.02, 132.90, 130.17, 129.01, 126.24, 125.21, 123.09, 55.59, 30.56; HRMS (ESI): $[M + H]^+$ calcd for $[C_{14}H_{18}N_2Se]$: 280.0485, found: 280.0482.

1-methyl-2-(phenylselanyl)-1H-benzo[d]imidazole (5n): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.5). The title compound was obtained as a brown liquid (88%, 126.6 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.2 Hz, 1H), 7.49-7.48 (m, 2H), 7.34-7.26 (m, 6H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.90, 143.54, 136.42, 132.31, 129.71, 128.32, 127.98, 123.35, 122.47, 119.81, 109.59, 31.86; HRMS (ESI): $[M + H]^+$ calcd for $[C_{14}H_{12}N_2Se]$: 288.0172, found: 288.0164.

2-((4-chlorophenyl)selanyl)-1-methyl-1H-benzo[d]imidazole (5o): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 3/1, R_f = 0.4). The title compound was obtained as a colorless liquid (80%, 128.5 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.2 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.31-7.23 (m, 5H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.71, 143.50, 136.45, 134.35, 133.67, 129.86, 126.40, 123.42, 122.50, 119.89, 109.58, 31.79; HRMS (ESI): $[M + H]^+$ calcd for $[C_{14}H_{11}ClN_2Se]$: 321.9782, found: 321.9776.

1-methyl-2-(p-tolylselanyl)-1H-benzo[d]imidazole (5p): Isolated by flash column chromatography (petroleum ether/ethyl acetate = 2/1, R_f = 0.5). The title compound was obtained as a colorless liquid (91%, 137.1 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 7.83-7.80 (m, 1H), 7.48-7.45 (m, 2H), 7.36-7.29 (m, 3H), 7.12-7.10 (m, 2H), 3.78 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.39, 138.45, 136.26, 133.04, 130.56, 123.94, 123.35, 122.59, 119.52, 109.55, 31.89, 21.16; HRMS (ESI): $[M + H]^+$ calcd for $[C_{15}H_{14}N_2Se]$: 302.0328, found: 302.0321.

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References and notes

1 (a) D. I. Shah, M. Sharma, Y. Bansal, G. Bansal, M. Singh, *Eur. J. Med. Chem.*, **2008**, 43, 1808-1812. (b) R. Rossi, G. Angelici, G. Casotti, C. Manzini and M. Lessi, *Adv. Synth. Catal.*, **2019**, 361, 2737-2803. (c) D. Kong, T. Huang, M. Wu and Q. Lin, *Org. Biomol. Chem.*, **2019**, 17, 830-834.

2 (a) I. Kawasaki, M. Yamashita and S. Ohta, *J. Chem. Soc., Chem. Commun.*, **1994**, 2085-2086. (b) I. Kawasaki, M. Yamashita and S. Ohta, *Chem. Pharm. Bull.*, **1996**, 44, 1831-1837. (c) Y.-Y. Hei, Y. Shen, J. Wang, H. Zhang, H.-Y. Zhao, M. Xin, Y.-X. Cao, Y. Li, S.-Q. Zhang, *Bioorg. Med. Chem.*, **2018**, 26, 2173-2185.

3 (a) I. Kawasaki, H. Katsuma, Y. Nakayama, M. Yamashita and S. Ohta, *Heterocycles*, **1998**, 48, 1887-1901. (b) Q. Liang, Y. Zhang, M. Zeng, L. Guan, Y. Xiao and F. Xiao, *Toxicol. Res.*, **2018**, 7, 521-528. (c) B. Shi, Z. Zhu, Y.-S. Zhu, D. Zhou, J. Wang, P. Zhou and H. Jing, *Org. Biomol. Chem.*, **2016**, 14, 2978-2984.

4 (a) I. Kawasaki, N. Taguchi, T. Yamamoto, M. Yamashita and S. Ohta, *Tetrahedron Lett.*, **1995**, 36, 8251-8254. (b) I. Kawasaki, N. Taguchi, T. Yamamoto, M. Yamashita and S. Ohta, *Chem. Pharm. Bull.*, **1997**, 45, 1393-1398.

5 S. Ohta, N. Tsuno, S. Nakamura, N. Taguchi, M. Yamashita, I. Kawasaki and M. Fujieda, *Heterocycles*, **2000**, 53, 1939-1955.

6 S. Ohta, N. Tsuno, K. Maeda, S. Nakamura, N. Taguchi, M. Fujieda, K. Futamura, T. Yoshida, M. Yamashita and I. Kawasaki, *Tetrahedron Lett.*, **2000**, 41, 4623-4627.

7 S. Ohta, T. Yamamoto, I. Kawasaki, M. Yamashita, Y. Nagashima, and T. Yoshikawa, *Chem. Pharm. Bull.*, **1994**, 42, 821-825.

8 V. Mathieu, E. Berge, J. Ceusters, T. Konopka, A. Cops, C. Bruyere, C. Pirker, W. Berger, T. Trieu-Van, D. Serteyn, R. Kiss and R. Robiette, *J. Med. Chem.*, **2013**, 56, 6626-6637.

9 (a) S. Tsuji, K. L. Rinehart, S. P. Gunasekera, Y. Kashman, S. S. Cross, M. S. Lui, S. A. Pomponi and M. C. Diaz, *J. Org. Chem.*, **1988**, 53, 5446-5453. (b) S. Sakemi and H. H. Sun, *J. Org. Chem.*, **1991**, 56, 4304-4307.

10 (a) X. Lei, Y. Wang, E. Fan and Z. Sun, *Org. Lett.*, **2019**, 21, 1484-1487. (b) D. J. Faulkner, *Nat. Prod. Rep.*, **1992**, 9, 323-364. (c) K. Bartik, J. C. Breakman, D. Daloze, C. Stoller, J. Huysecom, G. Vandevyver and R. Ottinger, *Can. J. Chem.*, **1987**, 65, 2118-2121.

11 (a) S. Nakamura, N. Tsuno, M. Yamashita, I. Kawasaki, S. Ohta and Y. Ohishi, *J. Chem. Soc., Perkin Trans. 1*, **2001**, 429-436. (b) S. Ohta, T. Yamamoto, I. Kawasaki, M. Yamashita, H. Katsuma, R. Nasako, K. Kobayashi and K. Ogawa, *Chem. Pharm. Bull.*, **1992**, 40, 2681-2685. (c) J. R. Lewis, *Nat. Prod. Rep.*, **1992**, 9, 81-101.

12 (a) B. Lin, C.-H. Lim and G. M. Miyake, *J. Am. Chem. Soc.*, **2017**, 139, 13616-13619. (b) C. Dai, Z.-Q. Xu, F. Huang, Z.-K. Yu and Y.-F. Gao, *J. Org. Chem.*, **2012**, 77, 4414-4419.

13 (a) D. Hu, M. Liu, H. Wu, W. Gao and G. Wu, *Org. Chem. Front.*, **2018**, 5, 1352-1355. (b) Z.-S. Gu, W.-X. Chen and L.-X. Shao, *J. Org. Chem.*, **2014**, 79, 5806-5811. (c) G. Roy and G. Mugesh, *J. Am. Chem. Soc.*, **2005**, 127, 15207-15217. (d) J.-R. Huang, Q.-R. Zhang, C.-H. Qu, X.-H. Sun, L. Dong and Y.-C. Chen, *Org. Lett.*, **2013**, 15, 1878-1881. (e) J. A. Jablonowski, K. S. Ly, M. Bogenstaetter, C. A. Dvorak, J. D. Boggs, L. K. Dvorak, B. Lord, K. L. Miller, C. Mazur, S. J. Wilson, T. W. Lovenberg, N. I. Carruthers, *Bioorg. Med. Chem. Lett.*, **2009**, 19, 903-907.

14 (a) N. J. Curtis and R. S. Brown, *J. Org. Chem.*, **1980**, 45, 4038-4040. (b) B. T. Phillips, D. A. Claremon, S. L. Varga, *Synthesis*, **1990**, 9, 761-763. (c) G. Chauviere, B. Bouteille, B. Enanga, C. Albuquerque, S. L. Croft, M. Dumas and J. Perie, *J. Med. Chem.*, **2003**, 46, 427-440.

15 I. M. Yonova, C. A. Osborne, N. S. Morrissette and E. R. Jarvo, *J. Org. Chem.*, **2014**, 79, 1947-1953.

16 A.-X. Zhou, X.-Y. Liu, Y. Ke, S.-C. Zhao and Y.-M. Liang, *Org. Biomol. Chem.*, **2011**, 9, 5456-5462.

17 (a) B. Y.-H. Tan, Y.-C. Teo, *Tetrahedron*, **2016**, 72, 6646-6653. (b) H.-L. Kao, C.-K. Chen, Y.-J. Wang and C.-F. Lee, *Eur. J. Org. Chem.*, **2011**, 9, 1776-1781. (c) C.-K. Chen, Y.-W. Chen, C.-H. Lin, H.-P. Lin, C.-F. Lee, *Chem. Commun.*, **2010**, 46, 282-284. (d) A. Correa, M. Carril and C. Bolm, *Angew. Chem. Int. Ed.*, **2008**, 47, 2880-2883.

18 (a) N.-B. Li, J. Yao, L. -X. Wang, J.-C. Wei, W. Liu, W. -Q. Liu, X.-H. Xu, Z.-W. Liang, *Inorg. Chem. Commun.*, **2018**, 98, 99-104. (b) S.-S. Wu, C.-T. Feng, D Hu, Y.-K. Huang, Z. Li, Z.-G. Luo, and S.-T. Ma, *Org. Biomol. Chem.*, **2017**, 15, 1680-1685. (c) D. Yang, K. Yan, W. Wei, J. Zhao, M. Zhang, X. Sheng, G. Li, S. Lu, and H. Wang, *J. Org. Chem.*, **2015**, 80, 6083-6092. (d) L.-X. Wang, N.-B. Li, H.-J. Wang, W. Liu, H.-P. Diao, X.-H. Xu, *Chin. J. Org. Chem.*, **2019**, 39, 1802-1807. (e) C. Xia, Z. Wei, Y. Yang, W. Yu, H. Liao, C. Shen, and P. Zhang, *Chem. Asian J.*, **2016**, 11, 360-366.

19 (a) C.-R. Liu, L.-H. Ding, *Org. Biomol. Chem.*, **2015**, 13, 2251-2254. (b) S. Sharma and A. Sharma, *Org. Biomol. Chem.*, **2019**, 17, 4384-4405. (c) L. Bettanin, S. Saba, C. V. Doerner, M. S. Franco, M. Godoi, J. Rafique, A. L. Braga, *Tetrahedron*, **2018**, 74, 3971-3980.

20 (a) S.-Q. Chen, Q.-M. Wang, P.-C. Xu, S.-P. Ge, P. Zhong and X.-H. Zhang, *Phosphorus & Sulfur & the Related Elements*, **2016**, 191, 100-103. (b) S. Zhang, P. Qian, M. Zhang, M. Hu, and J. Cheng, *J. Org. Chem.*, **2010**, 75, 6732-6735. (c) D. Yang, P. Sun, W. Wei, L. Meng, L. He, B. Fang, W. Jiang, and H. Wang, *Org. Chem. Front.*, **2016**, 3, 1457-1461. (d) W.-H. Bao, C. Wu, J.-T. Wang, W. Xia, P. Chen, Z. Tang, X. Xu and W.-M. He, *Org. Biomol. Chem.*, **2018**, 16, 8403-8407. (e) W.-H. Bao, M. He, J.-T. Wang, X. Peng, M. Sung, Z. Tang, S. Jiang, Z. Cao, W.-M. He, *J. Org. Chem.*, **2019**, 84, 6065-6071.

21 (a) L.-Y. Xie, S. Peng, J.-X. Tan, R.-X. Sun, X. Yu, N.-N. Dai, Z.-L. Tang, X. Xu, and W.-M. He, *ACS Sustainable Chem. Eng.*, **2018**, 6, 16976-16981. (b) W.-H. Bao, Z. Wang, X. Tang, Y.-F. Zhang, J.-X. Tan, Q. Zhu, Z. Cao, Y.-W. Lin and W.-M. He, *Chin. Chem. Lett.*, **2019**, DOI: 10.1016/j.cclet.2019.06.052. (c) C. Chen, P. Niu, Z. Shen, and M. Li, J. Electrochem. Soc., **2018**, 165, 67-74. (d) W. Ge and Y. Wei, *Green Chem.*, **2012**, 14, 2066-2070. (e) H. Zhang, X. Bao, Y. Song, J. Qu, B. Wang, *Tetrahedron*, **2015**, 71, 8885-8891.

22 (a) J. Chen, Z. Tang, R. Qiu, Y. He, X. Wang, N. Li, H. Yi, C.-T Au, S.-F Yin, and X. Xu, *Org. Lett.*, **2015**, 17, 2162-2165. (b) N. Li, J. Yao, L. Wang, J. Wei, W. Liu, W. Liu, X. Xu, Z. Liang, *Inorg. Chem. Commun.*, **2018**, 98, 99-104. (c) X. Wang, R. Qiu, C. Yan, V. P. Reddy, L. Zhu, X. Xu, S.-F Yin, *Org. Lett.*, **2015**, 17, 1970-1973. (d) L. Wang, N. Li, H. Wang, W. Liu, H. Diao, X. Xu, *Chin. J. Org. Chem.*, **2019**, 39, 1802-1807.

23 D. Singh, A. M. Deobald, L. R. S. Camargo, G. Tabarelli, O. E. D. Rodrigues, A. L. Braga, *Org. Lett.*, **2010**, 12, 3288-3291.

24 N. W. Gilman, W. Y. Chen, Inc., 4973599 USA, **1990**.

Highlights

► A convenient and metal-free protocol for the synthesis of 2-arylthio(seleno)imidazoles.

►This process is scalable and tolerates a wide spectrum of disulfides (diselenides).

► This method showed considerable advantages such as simple operation, wide functional group tolerance and good yields.

► A plausible mechanistic approach has also been proposed.

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Dear Editor,

No conflict of interest exists in the submission of this manuscript, and the manuscript is approved by all authors for publication. I would like to declare on behalf of my co-authors that the work described is original and has not been published previously, and not under consideration for publication elsewhere, in whole or in part. All the authors listed have approved the contents of the manuscript.

Sincerely yours,

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